

## APPLICATION OF SUPERCRITICAL CARBON DIOXIDE TO ENHANCE DISSOLUTION RATE OF BICALUTAMIDE

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**Abstract:** Bicalutamide solid dispersions were prepared by supercritical fluid method using carbon dioxide as a solvent. Approximately 8-fold dissolution improvement was noticed for system prepared with supercritical carbon dioxide containing Poloxamer 407 as a carrier, when compared to physical mixture. The system was characterized using scanning electron microscopy, X-ray powder diffraction and differential scanning calorimetry. We found that applying the supercritical fluid treatment led to significant decrease in bicalutamide crystals size and their partial amorphization. The studies confirmed that use of supercritical fluid technology might be efficient for dissolution rate enhancement of poorly water soluble drugs.

**Keywords:** bicalutamide, supercritical carbon dioxide, solid dispersion, dissolution, Poloxamer 407

Poorly water soluble active pharmaceutical ingredients (APIs) may undergo incomplete dissolution in gastrointestinal fluids and thus be only partially absorbed into systemic circulation. As it is reported, ca. 40% of commercialized APIs and almost 70% of potential new drugs are poorly water soluble (1). Formation of solid dispersions that leads to dispersion of insoluble APIs among well soluble polymeric matrix is potential approach to enhance their bioavailability. The processing methods like fast cooling from melting, spray drying or micronization, may result in crystalline drugs amorphization. However, solids are often characterized by combined properties, i.e. partially crystalline, containing stable and metastable forms and partially amorphous. The result of applied process can be very complexed and tough to control (2).

Bicalutamide (BCL) is a non-steroidal antiandrogen used in treatment of prostate cancer (3). It is administered orally as 50 mg tablets. Since the drug is practically insoluble in water (4 µg/mL at 37°C) (4) and has high membrane permeability (LogP 2.92) (5), it is assigned to class II according to

Biopharmaceutical Classification System (6). Its pK<sub>a</sub> = 12 is higher than the upper limit of intestinal fluids pH, therefore BCL solubility does not seem to be facilitated in any region of gastrointestinal tract (5). The BCL crystals exhibit polymorphism - forms I and II have already been identified (7-9). While form I referred as monoclinic is more stable than triclinic form II, the form II is 2.4-times more soluble than form I. Nevertheless, both polymorphs are very poorly soluble in aqueous media (10).

BCL dissolution rate can be improved by development of API-cyclodextrins complexes or formulation of solid dispersions. Complexation of BCL with β-cyclodextrin in 1 : 1, 1 : 2 and 1 : 5 w/w ratios was carried out by three techniques, i.e., solvent evaporation, spray-drying and kneading. The most significant improvement of drug dissolution rate was observed for 1 : 5 inclusion complex prepared by kneading (11).

BCL solid dispersions were formulated by hot melt extrusion, solvent evaporation or melting methods. Gavin et al. described the manufacture of BCL and polyvinylpyrrolidone K25 (PVP) systems in 1 :

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10, 2 : 10 and 3 : 10 w/w ratios prepared by hot melt extrusion. The drug dissolution enhancement was attributed to BCL amorphization and the extrudates' wettability improvement caused by PVP hydrophilic matrix (12).

The solvent evaporation method was applied for solid dispersions preparation containing BCL and PVP or Poloxamer® 407 and F68 (PLX) (13-15). The drug-carrier ratio was the most important factor affecting the drug dissolution rate. In particular, the highest dissolution rate was observed for solid dispersion prepared in 1 : 5 w/w ratio, for both carriers i.e., PVP K30 and PLX 407. This phenomenon may

be caused by transformation of crystalline BCL into amorphous form. The other study demonstrated that improvement of BCL dissolution rate was the most effective for the 1 : 1 BCL–Poloxamer® F68 solid dispersion prepared by melting method (15). The effect was attributed to partial amorphization of the API. Surprisingly, increase in Poloxamer® F68 quantity resulted in prolongation of BCL dissolution that was caused by the gelling of PLX.

Improvement in BCL dissolution rate was also achieved by solid dispersion prepared with Aeroperl® 300, a highly porous grade of spherically shaped fumed silica and hydrophilic Macrogol

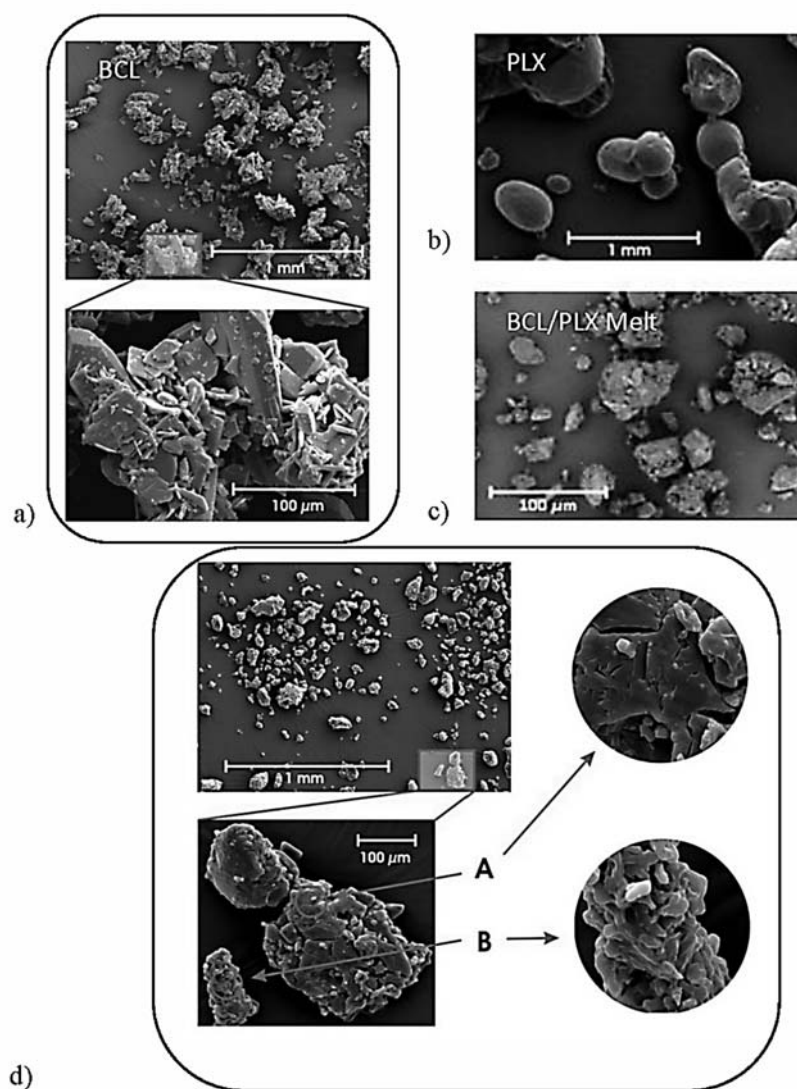


Figure 1. SEM micrographs of: a) Bicalutamide (BCL), b) Poloxamer® 407 (PLX), c) solid dispersion made by melting method (BCL/PLX Melt), d) solid dispersion made with supercritical CO<sub>2</sub> (BCL/PLX SCF)

Table 1. Properties of pure bicalutamide and the binary systems. Abbreviations: BCL - bicalutamide, PLX - Poloxamer, PhM - physical mixture, Melt - melting method, SCF - supercritical carbon dioxide method.

Sample	Appearance
BCL	white, crystalline powder
BCL/PLX PhM	white powder, crystals of BCL are visible
BCL/PLX Melt	white, waxy, easily pulverized
BCL/PLX SCF	white, free flowing powder

Table 2. The enthalpies  $\Delta H$  and temperatures  $T_{onset}$  (in parentheses) of tested samples. With the exception of PLX407 all of the determined values were normalized to the weight of bicalutamide.

Sample	$\Delta H$ [mJ/mg]	( $T_{onset}$ [°C])
BCL	-	113.0 (194.20)
PLX	129.0 (51.93)	-
BCL/PLX SCF	139.0 (50.34)	61.0 (159.90)
BCL/PLX PhM	92.3 (52.22)	150.0 (181.90)

Table 3. Kinetics data.

Sample	Equation constant	DE
BCL	0.39	8.13
BCL/PLX PhM	1.04	24.38
BCL/PLX Melt	2.26	39.79
BCL/PLX SCF	3.33	65.18

DE - dissolution efficiency

400. The API and Macroglol 400 were dissolved in an organic solvent - acetone, and then mixed with silica. After the solvent was evaporated, particles of amorphous BCL surrounded by Macroglol 400 were uniformly adsorbed within the silica pores. As a result, the dissolution rate of BCL was improved 15-fold in comparison to unprocessed active substance. The effect was attributed to amorphization of the API and the phase stabilization by the drug incorporated into Aeroperl® 300 pores, as well as by improvement of the particles wetting by the presence of Macroglol 400 (16).

In recent years, the supercritical fluid (SCF) technique was applied to solid dispersion formation. This method has become popular in the pharmaceutical sciences and recognizable by industry. Numerous applications, e.g., extraction of thermally sensitive substances, drug particles' size reduction, mixing and complexation (17-19) may be much easier with SCF technology. Carbon dioxide (CO<sub>2</sub>), is the most popular medium, since it is non-toxic, non-flammable, inexpensive, easy to remove and pos-

sesses low critical temperature and pressure (31.1°C and 73.8 bar). The molecule has linear shape (O-C-O), so its dipolar momentum is zero and the quadrupolar momentum is very small. Hence, the nonpolar (lipophilic) substances can be easily extracted from polar (hydrophilic) matrices simply by dissolution in supercritical CO<sub>2</sub> at relatively low temperature. Such properties enable supercritical carbon dioxide (scCO<sub>2</sub>) to replace organic solvents as well as prevent drug degradation (20, 21). Up to now the supercritical fluid technique was successfully applied for dissolution enhancement of carbamazepine (22), nifedipine (23) and furosemide (24).

The present study was aimed to improve solubility and dissolution rate of bicalutamide by preparation of solid dispersion using SCF and melting method. Poloxamer® 407, a low-meltable polymeric surfactant was chosen as a carrier. The effect of preparation method on drug dissolution was investigated. The solid dispersions and physical mixture containing BCL and PLX in 1 : 1 w/w ratio were characterized by scanning electron microscopy

(SEM), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC).

## EXPERIMENTAL

### Materials

Bicalutamide (BCL, Pharmaceutical Research Institute, Poland), Poloxamer® 407 (PLX, BASF, Germany), carbon dioxide in form of dry ice (Linde, Poland). All materials were of analytical grade.

### Procedures

Two methods, i.e., supercritical carbon dioxide method or melting method were used for preparation of bicalutamide and Poloxamer® 407 solid dispersions while the physical mixture was prepared by mixing with carrier in a mortar. Samples were prepared in 1 : 1 (w/w) drug to carrier ratio.

### Supercritical carbon dioxide method

The materials, BCL and PLX were loaded into high pressure reactor BR-300 (Berghof Products + Instruments GmbH, Germany) equipped with magnetic stirrer MR Hei-Standard (Heidolph Instruments, Germany) and thermometer CHY 700T (CHY Firemate Co., Taiwan). The calculated quantity of CO<sub>2</sub> in form of dry ice was placed in the reactor to achieve supercritical pressure of 130 bar at 60°C. Temperature, pressure, and mixing speed were monitored during the process.

### Melting method

Polymer was melted in a water bath and BCL was poured while stirring. Dispersion of BCL in

melted polymer was cooled down to the ambient temperature. After 24 h of storage in desiccator the solidified mass was crushed, pulverized and sieved through the 500 µm sieve.

### Characterization of solid dispersion

#### *Morphological analysis by scanning electron microscopy*

Particles were examined using scanning electron microscope S-4700 (Hitachi Inc., Japan). The powder was adhered to a sample holder by a double-sided carbon tape and coated with gold using the 208 HR sputter coater (Cressington Scientific, USA). The images were taken at the magnification of 50× and 400×.

#### *X-ray powder diffraction analysis*

The diffraction pattern was recorded in terms of 2θ at a range of 2° - 60° using PW 1830 diffractometer (Philips, The Netherlands) equipped with nickel filtered Cu-Kα radiation ( $\lambda = 1.5406 \text{ \AA}$ ). Diffraction patterns used later for Rietveld analysis were recorded with the rate of 0.02°/10 s. Analyses were performed in MAUD (25) environment, FITYK (26) was used as auxiliary software for data preparation.

#### *Differential scanning calorimetry analysis*

The measurements were performed using DSC7020 calorimeter (Hitachi Inc., Japan) equipped with dedicated electric cooling unit. The apparatus was calibrated using indium and tin standards. The analyses were performed in nitrogen atmosphere with a flow rate of 50 mL/min. The 6.8 - 8.1 mg of samples were placed in aluminum pans

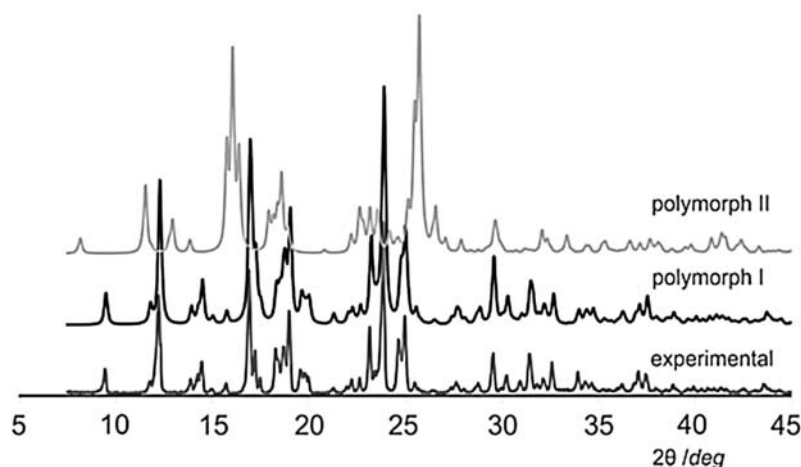


Figure 2. Experimental XRPD pattern of bicalutamide sample, simulated patterns of polymorph I and polymorph II. Structural data for polymorphs I and II were taken from 2014 CCDC database

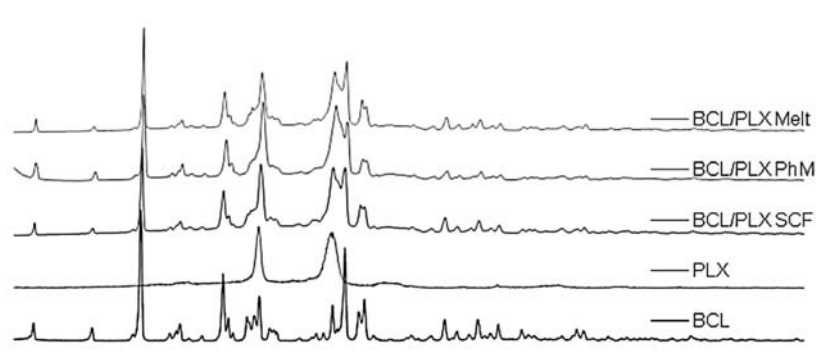


Figure 3. Diffractograms of: crystalline bicalutamide (BCL), Poloxamer® 407 (PLX), solid dispersions BCL/PLX SCF and BCL/PLX Melt, physical mixture of bicalutamide and PLX (BCL/PLX PhM), Presented intensities are not to scale

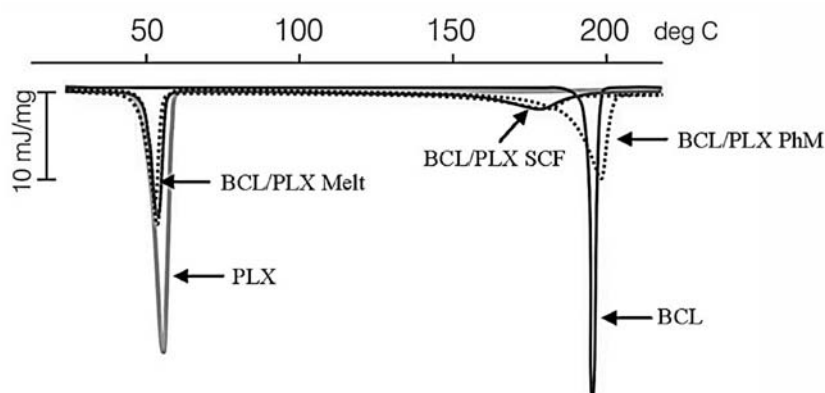


Figure 4. DSC endothermic curves of studied samples: crystalline BCL (green line), PLX (solid gray line), physical mixture (blue dotted line), BCL/PLX melting method (purple dotted line) and  $\text{scCO}_2$  treated product (red line)

and sealed. The following thermal protocol was used: equilibrating at 25°C for 15 min, then heating to 220°C, except PLX, which was heated to 200°C, at heating rate of 10°C/min. With the exception of PLX all determined  $\Delta H$  values of samples within the study were normalized to the weight of BCL.

#### Solubility studies

An excess of drug or binary system was dispersed in 25 mL of distilled water in a conical flask. The suspension was shaken at room temperature using the KS 130 Basic shaker (IKA, Germany) for at least 24 h to achieve the equilibrium solubility. Samples were centrifuged at 3600 rpm for 30 min in the MPW 221 apparatus (MPW, Poland) and filtered through a 0.2  $\mu\text{m}$  membrane filter. The diluted samples were assayed at 270 nm with UV-VIS spectrophotometer V-500 (Jasco Analytical Instruments, USA). The reported data represents the averages from three series of measurements.

#### Dissolution rate studies

Dissolution studies were carried out using the method recommended by the FDA for BCL tablets, i.e. USP type II apparatus (paddle) at 50 rpm, 1000 mL of water containing 1% SLS at  $37 \pm 0.5^\circ\text{C}$ . The analysis was performed in the SR8 Plus type II Dissolution Test Station (Hanson Research, USA). A certain amount of powder samples, i.e., solid dispersions, physical mixtures or pure drug, equivalent to 50 mg of active substance, were poured into the beakers. 5 mL of solution were withdrawn from each dissolution vessel at predefined intervals, filtered, diluted and assayed spectrophotometrically at  $\lambda = 272 \text{ nm}$ . After collection of the each sample the dissolution medium was replaced with the same volume of dissolution medium. The tests were carried out in triplicate. The dissolution data were analyzed by Open Source software KinetDS 3.0 with standard settings including non-linear regression methods. Different models i.e., zero order, first order, second

order, third order, Korsmeyer-Peppas model,  $y = a \cdot \ln(x) + b$  model, Weibull models, Hixson-Crowell, Higuchi, Baker-Lonsdale, Michaelis-Menten, Hill, were evaluated to found the best fit to obtained data (27).

## RESULTS AND DISCUSSION

### *Effects of preparation methods on samples physical state*

The both methods i.e., supercritical carbon dioxide (SCF) and melting (Melt) were suitable for preparation of BCL solid dispersions, however they impacted the samples properties. Referring to table 1, solid dispersion prepared by SCF was in form of freely flowing powder, while prepared by melting method was a little waxy but easy to pulverize.

The SEM micrographs of raw materials and solid dispersions are compared in Figure 1. Bicalutamide (Fig. 1a) appears as aggregates composed of plate-like crystallites of different size, from 15  $\mu\text{m}$  up to 200  $\mu\text{m}$  in length. The individual plates exhibit shape of elongated hexagons. Poloxamer® 407 (Fig. 1b) is in form of smooth particles of droplet-like elliptical shape. The solid dispersion obtained by melting (Fig. 1c) demonstrates aggregates with sharp edges covered by carrier, however a fraction of uncovered crystals is also noticeable. Reduction of particle size was observed. The solid dispersion prepared by SCF method (Fig. 1d) shows

random aggregates of small block-like objects with edges rounded as if they were covered with polymer layer. It is worth to emphasize that significant fraction of the grains has smaller size than the drug substance presented in Figure 1a. In our opinion during SCF process PLX covered the drug crystals entirely and after cooling and depressurization a partial recrystallization of BCL occurred.

In the crystallographic databases two polymorphs of BCL are listed. The first reference structure corresponds to plate-like crystals (7) while the second to the prism-like ones (3). The micrograph in Figure 1a presents plate-like crystals of the non-treated BCL, which suggests that structure of polymorph I is dominant. The finding is fully consistent with the set of diffraction patterns presented in Figure 2.

The XRPD patterns of pure BCL, PLX, solid dispersions prepared by the both methods and corresponding physical mixture are shown in Figure 3. Broad peaks in PLX diffractogram are typical for polymeric substances, in which structural elements show only short-range ordering. These peaks were mathematically removed from diffraction patterns of binary systems with right proportion to their weight fraction before further interpretation of powder diffractograms. The curve obtained for physical mixture indicate unchanged diffraction pattern of BCL. This is confirmed by analysis of diffractogram appearing after removal of PLX results from the curve of physical mixture. The diffraction pattern of

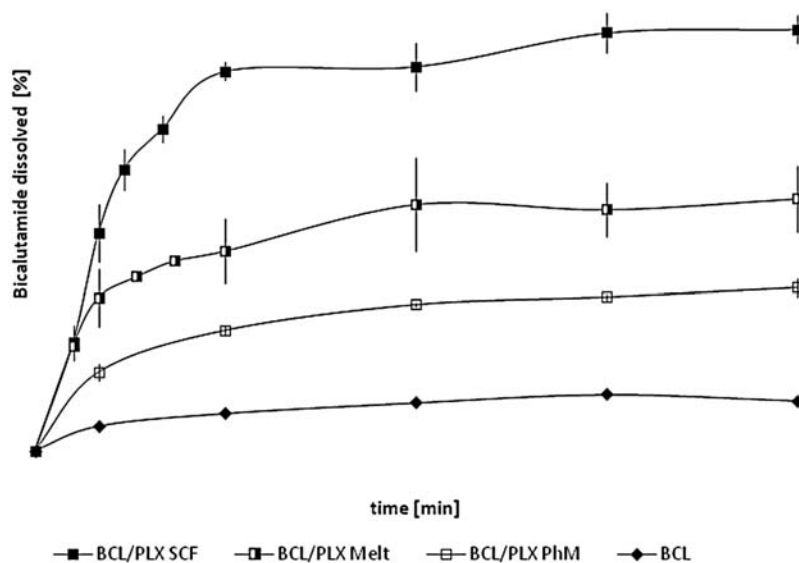


Figure 5. Dissolution rate profiles tested for non-processed bicalutamide (BCL), solid dispersions (BCL/PLX) prepared by melting (Melt), the supercritical carbon dioxide method (SCF) or by physical mixing (PhM). Method: Ph. Eur. ap. 2, 50 rpm, 1000 mL of 1% SLS solution in water



the SCF treated sample becomes more complex. It reveals that BCL peaks are broader than observed in the unprocessed substance. The Scherrer formula was used to determine mean diameter of monocrystral zones:

$$D = \frac{0.89 \lambda}{B \cos \theta}$$

where:  $D$  stands for the mean diameter of monocrystral,  $\lambda$  for wavelength of X-ray used,  $B$  is half-width of a peak and  $\theta$  stands for the diffraction angle.

SCF process leads to decrease in monocrystalline BCL domains size from  $230 \pm 7$  nm before, to  $170 \pm 5$  nm after treatment. The comparison of the XRPD data with SEM micrographs points to the fact that almost all individual grains of BCL and BCL/PLX SCF are much larger than monocrystals, and thus they are considered as polycrystalline aggregates. At least two mechanisms may be responsible for lowering of BCL crystal size. The first is dissolution and subsequent quick recrystallization of the drug during treatment by SCF. It is supported by Figure 1d which shows the aggregates composed of tiny crystals, which are all covered with PLX and stack together. However, the smallest visible crystals are about 20-times larger than the mean monocrystallite size. The recrystallization was so quick that it stopped shortly after nucleation of BCL crystals. It is worth noting that PLX prevented formation of larger BCL crystals. Strong interactions between BCL and PLX are also suggested by the fact that BCL recrystallizes in the shape of block-like grains (cf. Fig 1d).

The DCS curves of the pure drug, the physical mixture and the solid dispersions are shown in Figure 4. The DSC curve of crystalline BCL exhibited a single endothermic response corresponding to melting of the drug. BCL reveals significant changes of the melting temperature in the presence of PLX. Drug and carrier interact strongly even when physically mixed. In this case (cf. Table 2) the onset temperature goes down by  $12^{\circ}\text{C}$  (from  $194.2$  to  $181.9^{\circ}\text{C}$ ). Sample treated by SCF is characterized by onset temperature as low as  $159.9^{\circ}\text{C}$ , which is ca.  $34^{\circ}\text{C}$  lower than the onset temperature of pure bicalutamide. The DSC curve of BCL/PLX Melt is similar to SCF curve.

The melting energies  $\Delta H$  recalculated for the pure drug and obtained for the above mentioned physical mixture and solid dispersion are  $150.0$  mJ/mg and  $61.0$  mJ/mg, respectively. Such a considerable difference ( $89.0$  mJ/mg) and a wide temperature shift indicate destabilization of the crystal structure of BCL and its partial amorphization. It means that morphology of both PLX and BCL has

been changed, which has previously been illustrated in SEM images. The above results indicate that the treated sample contains BCL as amorphous, small, recrystallized grains and some unchanged, crystalline large grains.

### Improvement of bicalutamide dissolution rate

The determined solubility of bicalutamide in water at  $25^{\circ}\text{C}$  was low, i.e.,  $3.7$   $\mu\text{g/mL}$ . Poloxamer® 407 as nonionic surfactant with HLB value 18-23 being usually used as a solubilizer for many active ingredients should improve the solubility of BCL. However, in case of physical mixture, solubilizing effect of PLX on BCL was only slightly pronounced. The solubility of BCL from solid dispersion prepared by SCF method was greater than that of pure drug by a factor of 2.8.

The results of dissolution studies were in agreement with solubility data (Fig. 5). Importantly, in case of solid dispersions the use of PLX led to improvement of dissolution rate; the highest amount of BCL was dissolved from solid dispersion prepared by SCF method. After 1 h of testing, the amount of dissolved BCL was 1.7-times greater than from samples prepared by melting method and 8-times greater than from pure drug. At the same time only 30% of drug dissolved from physical mixture. The solid dispersion prepared by SCF method exhibited also higher burst release - 70,9% of drug after 15 min, twice greater than in the case of solid dispersion prepared by the melting method. Among all evaluated kinetic models the best fitting were found for Korsmeyer-Peppas model. Using it, the dissolution rate constants were determined. In Table 3 kinetic data obtained for solid dispersions systems, physical mixture as well as pure drug are presented. The s data confirm that the SCF method allowed to enhance the dissolution of BCL in more effective way than melting method.

The differences among dissolution profiles of BCL solid dispersion were mostly resulted from wetting effect of hydrophobic drug crystals surrounded by carrier's hydrophilic particles. The other reasons of dissolution profiles enhancement was reduction of particles size by SCF method and partial amorphization of BCL crystals.

### CONCLUSIONS

Two methods: supercritical fluid method and melting method were used for preparation of solid dispersions containing bicalutamide and Poloxamer® 407. The formulations were investigated using scanning electron microscopy, differential

scanning calorimetry as well as X-ray powder diffraction analyses. The SCF as solvent-free method proved to remarkable increase in the bicalutamide solubility and dissolution characteristics. The effects are attributed to the reduction of the size of drug crystals and partial amorphization what was confirmed by SEM, DSC and X-ray studies.

Application of melting method for preparation of solid dispersion was not satisfactory for BCL solubility and dissolution rate enhancement.

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